Foreword

Identifying Human Teratogens: An Update

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J Pediatr Genet 2015;4:39–41.

A *human teratogen* is an agent that alters the growth or structure of the developing embryo or fetus, thereby causing birth defects. The first human teratogen identified in 1941 by an ophthalmologist, Norman Gregg, was maternal rubella infection in pregnancy, which produced a triad of defects (cataracts, heart malformations, and deafness) in the infants.[1] Following the identification of thalidomide, an antinauseant, as a major human teratogen causing severe birth defects in 1961,[2] research in teratology began to expand and there was increased awareness of the possible teratogenic impact of maternal exposures during pregnancy.

Several factors that determine the teratogenicity of an exposure have been set forth as the principles of teratology by Wilson,[3] guiding researchers in the study and understanding of teratogenic agents. These include, but are not limited to, the following: Abnormal development produced by a teratogenic exposure is manifested as death, malformation(s), growth retardation, or a functional disorder. These include neurologic impairments, such as mental retardation, and long-term effects on cognition and behavior that may appear later in childhood. A second principle of teratology states that susceptibility to teratogenesis varies with the developmental stage at the time of exposure, and a third claims that manifestations of abnormal development depend on dose and duration of a teratogenic exposure. These indicate that not all exposures deemed as teratogenic are actually teratogenic all the time; the timing and dose of a particular exposure during pregnancy often determine the kind and extent of its teratogenic potential. The embryonic period, during which organogenesis takes place, occurs between implantation at around 14 days to around 60 days postconception. This is usually the most sensitive period to teratogenesis when exposure to a teratogenic agent has the greatest likelihood of producing a malformation. For example, administration of many established major teratogenic drugs, such as isotretinoin, valproic acid, warfarin, or high-dose methotrexate, in specific gestational windows in the first trimester is associated with a high risk of having a baby with a congenital malformation, but the risk significantly decreases in the second or third trimesters of pregnancy. In some cases, several periods of susceptibility may exist for a single organ, such as in the case of craniosynostosis, an abnormality that occurs as a result of premature fusing of cranial sutures. Also, for some teratogens, a level of exposure exists below which probably no demonstrated harmful embryonic effect occurs, such as in the case of methotrexate, a folic acid antagonist.[4]

Another teratology principle states that susceptibility to a teratogenic exposure also depends on the fetal and maternal genotype. Genetic predisposition to the effects of several teratogenic exposures has been intensively studied. For example, embryonic exposure to cigarette smoke has been established as a risk factor for orofacial clefts[5] and gastroschisis,[6] but even higher risks were found for cleft palate among the offspring of maternal smokers in the presence of a rare transforming growth factor α (*TGFA*) genotype[7] or a variation in the nitric oxide synthase (*NOS3*) gene in the infant.[8] The genetic basis underlying susceptibility to fetal alcohol syndrome and abnormal glucose metabolism-induced birth defects have also been linked to certain maternal and fetal gene variants.[9] Specifically with regard to drug metabolism, genetic variation in maternal metabolism of certain antiepileptic medications may predispose her infant to the development of birth defects.[9,10]

Experimental animal teratology studies performed on rodents are critical in determining the risk or safety in pregnancy of a particular agent, and are usually used by industry and regulatory agencies as a first step before a specific agent is approved for marketing, such as in the case of medications. However, it is sometimes difficult to extrapolate results from available animal studies to humans in part due to the relevance of the dose utilized and in part due to species differences in response to a medication. Experimental teratology studies or randomized controlled trials in human pregnancy are rarely permitted because of ethical reasons.

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Issue Theme Prenatal Exposures and Short and Long Term Developmental Outcomes; Guest Editors: Sura Alwan, PhD and Christina D. Chambers, PhD, MPH

DOI http://dx.doi.org/10.1055/s-0035-1556745.
ISSN 2146-4596.

Therefore, to determine whether an exposure is teratogenic in humans, observational studies are usually the method that is used to evaluate risk or safety. If these are performed at all, often the results are not available until many years after an agent has been marketed for use.[11] These include descriptive studies such as case reports, which are published reports of individual cases of birth defects in an infant exposed prenatally to the agent of interest, raising hypotheses about potential causality, or clinical case series, which track several affected infants with known common exposure histories, and determine whether a characteristic malformation pattern exists. Many major human teratogens, such as thalidomide, isotretinoin, rubella, and fetal alcohol syndrome, have been identified using clinical series.

Analytical observational studies, on the other hand, include cohort studies, which measure the frequencies of outcomes in exposed and unexposed (control) pregnancies. They can be prospective in nature, whereby exposures are recorded during pregnancy without knowledge of the outcomes. Data for prospective cohort studies can be obtained either for an entire population in a comprehensive and ongoing fashion (population-based) or through more focused studies relying on volunteers, such as through the efforts of one or more teratogen information services (exposure cohort). Retrospective record-linkage cohort studies are usually collected for administrative purposes (e.g., as prescription records or hospital discharge summaries) at the time a medical service is provided and then subsequently electronically linked to birth outcomes on a case-by-case basis. The third type of analytical epidemiological studies is case-control studies, which measure the frequency of exposure in the pregnancies of mothers of babies with (cases) or without (controls) birth defects. Exposure information in case-control studies is usually collected retrospectively through interviews or questionnaires given to mothers. These investigations are very useful for studying rare outcomes such as specific birth defects but may be limited by recall bias. Reproducibility of associations of a certain teratogenic exposure with an adverse outcome, using different types of observational studies, has been crucial in providing evidence in support of causality for many teratogens, particularly those with more moderate magnitude of effects.

Our goal for this special issue in *the Journal of Pediatric Genetics* is to present readers with emerging new data on prenatal exposures affecting short- and long-term developmental outcomes that may help guide clinicians and patients in considering the risks and benefits of various treatments. We begin with an update on the teratogenicity of maternal mycophenolate mofetil, an immunosuppressant that is frequently used in patients who have received solid organ transplants. In their paper, Coscia et al provide recent evidence from the literature, namely case reports and case series, of a recurrent pattern of malformations associated with maternal mycophenolate mofetil treatment during the first trimester of pregnancy. The authors strongly advise that pregnancy should be avoided while on this medication, and that providers and their patients consider modification of treatment prior to conception or when an unplanned pregnancy is discovered.

The next article in this issue by Yazdy et al reviews recent data regarding the effect on the fetus of maternal use in pregnancy of the most common prescription pain medications, opioid analgesics. The authors report on first-trimester opioid use and an increased risk of birth defects, including neural tube defects and congenital heart defects. The authors also review adverse fetal effects associated with maternal treatment anytime in pregnancy, such as poor fetal growth, preterm birth, and neonatal abstinence syndrome. It is therefore important that health care providers discuss these recent findings with their patients and explain the potential risks and benefits of taking these medications during pregnancy.

Teratogenic exposures are not necessarily always medications, infections, chemicals, or physical agents that a woman may encounter in her pregnancy. The teratogenic exposure may also be a preexisting chronic or physical condition, such as excess body weight. Iessa and Berard's update on prepregnancy maternal obesity in pregnancy summarizes interesting data on potential associations with birth defects, and other adverse outcomes, such as macrosomia or fetal death. This review also presents evidence on maternal obesity and the possible association with poor neurodevelopmental outcomes.

The next two articles of the special issue specifically focus on the effect of psychotropic and antiepileptic drugs (AEDs) on long-term cognitive and behavioral phenotypes in the offspring. The most frequently used class of antidepressant medications, selective serotonin reuptake inhibitors (SSRIs), has been a hot topic of interest over the past 10 year with regard to their use during pregnancy. Research results in the field have been widely conflicting, though most studies agree that a small teratogenic effect of these medications cannot be ruled out. Many AEDs, on the other hand, are established teratogens that adversely affect embryonic development when administered early in pregnancy. The papers in this special issue by Boukhris and Berard, and Gerard and Meador that cover these two drug classes review recent investigations into the effect of SSRIs and AEDs on neurodevelopment, with specific focus on autism spectrum disorders. The authors also touch on possible mechanisms of cognitive teratogenesis with regard to genetic susceptibility to SSRIs and AEDs. In the final paper in this special issue, Alwan and Hamamy present a review of maternal iron deficiency during pregnancy, suggesting that it may increase the risk for several adverse outcomes, such as fetal growth restriction, obesity, and high blood pressure in the offspring later in life, as well as neurobehavioral abnormalities.

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